CLINICAL GASTROENTEROLOGY AND HEPATOLOGY 2004;2:22–30

Polymorphism of Interleukin-1β Affects the Eradication Rates of *Helicobacter pylori* by Triple Therapy

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Background & Aims: Polymorphism in interleukin-1β (*IL-1β*) is associated with intragastric pH levels in *Helicobacter pylori*–positive subjects. Intragastric pH levels affect the activity of antibiotics against *H. pylori* in the stomach. The aim of this study was to investigate whether *IL-1β* polymorphism is associated with eradication rates of *H. pylori* by triple therapy with a proton pump inhibitor (PPI), amoxicillin, and clarithromycin. **Methods:** Three hundred thirty-six patients infected with *H. pylori* completed treatment with omeprazole, 20 mg, or lansoprazole, 30 mg twice daily; clarithromycin, 200 mg 3 times daily; and amoxicillin, 500 mg 3 times daily, for 1 week. *IL-1β*-511 and *CYP2C19* genotypes of patients and sensitivity of *H. pylori* to clarithromycin and amoxicillin were determined. **Results:** Logistic regression analysis showed that the *IL-1β*-511 polymorphism, as well as *CYP2C19* genotype of patients and clarithromycin-resistance of *H. pylori*, was associated with successful eradication. Eradication rates for *H. pylori* were 77.3% (75 of 97; 95% confidence interval, 67.5–84.6), 89.6% (147 of 164; 95% confidence interval, 83.9–93.1), and 94.7% (95% confidence interval, 86.9–98.5) in patients with the C/C, C/T, and T/T genotypes of *IL-1β*-511, respectively ($P = 0.0014$). **Conclusions:** *IL-1β*-511 polymorphism is one of the determinants of successful eradication of *H. pylori* using triple therapy with a PPI, amoxicillin, and clarithromycin, together with *CYP2C19* genotype and bacterial resistance to clarithromycin.

Helicobacter pylori infection is associated with upper-gastrointestinal diseases, including peptic ulcer disease, gastric adenocarcinoma, and gastric mucosa–associated lymphoid tissue lymphoma.[1–3] Indications for eradication of the infection are continually expanding and now include not only conditions in which there is definitive proof of benefit, such as peptic ulcer disease, gastric mucosa–associated lymphoid tissue lymphoma, and prevention of recurrence of gastric cancer after mucosal resection of early lesions,[4–6] but also conditions in which the benefit is less defined, such as nonulcer dyspepsia, prevention of gastric adenocarcinoma, and long-term use of proton pump inhibitors (PPIs). The ever-expanding use of eradication therapy calls for elucidation of factors associated with success or failure of such treatment. This would help in designing better therapeutic strategies and better identification of patients needing treatment.

The most commonly prescribed treatment regimen for eradication of infection caused by *H. pylori* is based on triple therapy with a PPI and 2 antibiotic agents, such as amoxicillin, clarithromycin, and metronidazole.[7] Cure rates achieved by this regimen have been reported to be ~85%–90%.[8] An eradication failure rate of 10%–15% has been reported by most studies. This poses a significant clinical problem that has implications for the wider dissemination of this form of antibiotic treatment.

One of the roles of PPIs in the PPI-based therapy is to increase the stability and bioavailability of the antibiotics by elevating intragastric pH to neutral levels. PPIs are substitutes of benzimidazole and are metabolized mainly in the liver by *S*-mephenytoin 4′-hydroxylase.[9] The gene encoding this enzyme (*CYP2C19*) recently was found to be polymorphic,[10–12] and various mutations have been described in different ethnic groups (http://www.imm.ki.se/CYPalleles/cyp2c19.htm). In Japanese populations, *CYP2C19* variations are determined largely by the combination of 2 point mutations, $CYP2C19_{m1}$ in exon 5 (m1) and $CYP2C19_{m2}$ in exon 4 (m2).[11]

Abbreviations used in this paper: ^{13}C-UBT, carbon 13–labeled urea breath test; DU, duodenal ulcer; GU, gastric ulcer; hetEM, heterozygous extensive metabolizer; homEM, homozygous extensive metabolizer; IL-1β, interleukin-1β; PCR, polymerase chain reaction; PM, poor metabolizer; PPI, proton pump inhibitor; RFLP, restriction fragment length polymorphism; RUT, rapid urease test; wt, wild type.

1542-3565/04/$30.00
PII: 10.1053/S1542-3565(04)00288-X

Based on these polymorphisms, it is possible to classify subjects into 3 distinct phenotypes: homozygous extensive metabolizers (homEMs), heterozygous extensive metabolizers (hetEMs), and poor metabolizers (PMs).[13] In homEMs, both copies of the gene have no mutations (wild type [wt]), and normal levels of the enzyme can be generated. In hetEMs, 1 copy is mutated in the coding region of *CYP*2C19, whereas the other has no mutations and enzyme can be generated; enzyme levels are slightly lower than those of homEMs. In PMs, both copies are mutated, and normal enzyme levels cannot be generated, resulting in deficiency of enzyme activity.[14] Frequencies of homEM, hetEM, and PM genotypes in Japanese population are ~35%, 50%, and 15%, respectively.[15–18] Recently, plasma levels of PPIs and their acid inhibitory effects have been found to depend on *CYP*2C19 polymorphisms,[19–23] and eradication rates using a PPI-based regimen have differed among patients with different *CYP*2C19 genotypes.[17,18,24–26] The eradication rate of *H. pylori* using a PPI-based therapy in patients with a PM or hetEM genotype of *CYP*2C19 is greater than that in those with the homEM genotype. These observations suggest that intragastric pH levels during eradication therapy could be considered one of the determinants of success or failure of eradication of *H. pylori*, as indicated previously by Labenz et al.[27]

H. pylori–induced inflammation is mediated by a variety of proinflammatory and anti-inflammatory cytokines that are up-regulated in the presence of a bacterium's lipopolysaccharide, urease, and toxins.[28–31] One of the key cytokines that has increased levels in the gastric mucosa in this process is interleukin-1β (IL-1β).[31] This cytokine is important in initiating and amplifying inflammatory responses against the bacterium and also is a potent inhibitor of gastric acid secretion.[32–34] We previously reported that IL-1β has an important role in acid suppression caused by *H. pylori* infection.[35,36] The IL-1β gene (*IL-1β*) encoding IL-1β is highly polymorphic, and several diallelic polymorphisms have been reported in the promoter region (C/T transition at −511 and T/C transition at −31) and exon 5 (C/T transition at +3954).[37–40] However, in the Japanese population, the *IL-1β*-511 polymorphism (which is near total linkage disequilibrium with the polymorphism at the −31 locus) is most important because of the high frequency of the variant T allele.[41–43] Genotypic frequencies of *IL-1β*-511 C/C, C/T, and T/T in the Japanese population are ~30%, 50%, and 20%, respectively.[41,42,44,45] This polymorphism has been associated with increased IL-1β production in *H. pylori*–infected gastric mucosa[43] and gastric hyposecretion in Caucasian and Japanese populations.[40,42,46] The gastric hyposecretion is thought to be related closely to risks for the development of gastric cancer.[47] Gastric juice pH levels in *H. pylori*–positive subjects with the *IL-1β*-511 T/T or C/T genotypes are significantly greater than those in subjects with the *IL-1β*-511 C/C genotype[42,46]; therefore, the former genotypes were reported to increase the risk for the development of noncardiac gastric cancer.[40,48,49]

In this study, we determined whether *IL-1β* polymorphisms had an effect on eradication rate using a PPI-based triple therapy with reference to the *CYP*2C19 genotype of patients and sensitivity of *H. pylori* to antimicrobial agents.

Methods

Subjects and Study Protocol

Study subjects consisted of 350 patients with gastric ulcer (GU; n = 110), duodenal ulcer (DU, n = 87), or gastritis only (n = 153). Mean age and weight of patients were 50.0 ± 9.9 (SD) years and 62.2 ± 9.1 kg, and 299 were men. These patients had endoscopically and histologically proven peptic ulcer or active chronic gastritis, and all were *H. pylori* positive on the basis of rapid urease test (RUT) and culture results and histological characteristics, described next.

For eradication of *H. pylori*, 20 mg of omeprazole twice daily (n = 175) or 30 mg of lansoprazole twice daily (n = 175), 200 mg of clarithromycin 3 times daily, and 500 mg of amoxicillin 3 times daily were administered for 1 week. Patients were assigned randomly to administration of omeprazole or lansoprazole. In addition, patients with GU or DU were administered a daily dose of 20 mg of omeprazole or 30 mg of lansoprazole for 5 to 7 weeks after the triple therapy. Endoscopic examination and determination of *H. pylori* status were performed before and 1 month after the end of all treatments, including a PPI administered alone. Compliance with therapy was assessed by pill counting. No patient consumed extensive amounts of alcohol. No patient had taken any drug at least 1 week before or during the study. Throughout the study period, investigators involved in the assessment of *H. pylori* eradication were unaware of *IL-1β* genotype, *CYP*2C19 genotype, and clarithromycin-resistance test results. The study protocol was approved by the Human Institutional Review Board of Hamamatsu University School of Medicine (Hamamatsu, Japan), and written informed consent was obtained from each patient before participation in the study.

Endoscopic Examination and Determination of *H. pylori* Infection and Its Sensitivity to Clarithromycin and Amoxicillin

During gastroduodenoscopy, several biopsy specimens from both the antrum and corpus of the greater curvature were obtained for RUT, bacteriological culture, histological examination, and polymerase chain reaction (PCR) analysis. For RUT, biopsy specimens were inoculated into the Modified

Rapid Urease Test (Tokushumenekikenkyujo Co., Tokyo, Japan) or Helicocheck (Otsuka Co., Tokushima, Japan). A positive result was recorded when the color changed from yellow to pink within 24 hours.

For bacterial culture and antimicrobial sensitivity testing, biopsy samples were inoculated onto agar plates developed by Dent and McNulty[50] and incubated at 37°C under microaerophilic conditions for up to 7 days. Colonies were identified as *H. pylori* on the basis of morphological characteristics in Gram stains, oxidase and catalase tests, and RUT results. They then were subcultured to determine minimum inhibitory concentrations of amoxicillin and clarithromycin by means of the agar dilution method. Cutoff concentrations used to define resistance were >0.5 μg/mL for amoxicillin and >1.0 μg/mL for clarithromycin.[51] Point mutations associated with clarithromycin resistance of *H. pylori*, i.e., adenine to guanine mutation at 2143 (A2143G) or 2144 (A2144G), were determined by PCR–restriction fragment length polymorphism (RFLP) analysis of genomic DNA extracted from gastric tissue samples, as previously reported.[52] When the minimum inhibitory concentration of clarithromycin was > 1.0 μg/mL or the A2143G or A2144G mutation was detected, the strain was considered clarithromycin resistant. In addition, tissue samples were stained with hematoxylin-eosin and Giemsa and examined histopathologically for the presence of *H. pylori*. All biopsy specimens were examined by the same pathologist, who was unaware of any clinical information regarding the patients. All patients also underwent a carbon 13–labeled (^{13}C)-urea breath test (UBT). Eradication of *H. pylori* was judged based on results of culture, histological examination, RUT, and ^{13}C-UBT. When all these tests yielded negative results 1 month after treatment, eradication of *H. pylori* was judged to have been achieved. When any 1 of these tests yielded a positive result, failure to cure *H. pylori* infection was diagnosed.

PCR-RFLP Analysis for *IL-1β*-511 and *CYP*2C19 Genotype Status

DNA was extracted from patients' leukocytes or gastric biopsy samples by using a commercially available kit (IsoQuick; Micro Probe Co., Garden Grove, CA). Genotyping of the *IL-1β*-511 polymorphism was determined using a PCR-RFLP method, as previously reported.[37,39,42] Genotyping procedures identifying *CYP*2C19 wild-type (wt) gene and the 2 mutated alleles, $CYP2C19_{m1}$ (m1) in exon 5 and $CYP2C19_{m2}$ (m2) in exon 4, also were performed using a PCR-RFLP method with allele-specific primers, described by de Morais et al.,[10–12] with minor modifications, described by Kubota et al.[16]

Statistical Analysis

Numerical values are given as mean ± SD. Statistically significant differences in mean age; body weight; and clarithromycin-sensitive/clarithromycin-resistant, male/female, homEM/hetEM/PM, and GU/DU/gastritis-only ratios among the different *IL-1β*-511 genotype groups were determined using 1-way analysis of variance or χ^2 test. Statistical significance of parameters associated with eradication of *H. pylori* in relation to the independent effects of confounding factors, such as *IL-1β*-511 genotype status, *CYP*2C19 genotype status, body weight, age, sex, GU/DU/gastritis-only, lansoprazole/omeprazole, and clarithromycin-resistant/clarithromycin-sensitive status was assessed by means of logistic regression analysis. Sex, GU/DU/gastritis-only, lansoprazole/omeprazole, clarithromycin-sensitive/clarithromycin-resistant, *CYP*2C19 genotype status (homEM, hetEM, PM), and *IL-1β*-511 genotype status (C/C, C/T, T/T) were entered as categorical variables, and body weight and age were entered as continuous variables in this analysis. Whether *H. pylori* eradication rates differed among the different genotype groups was determined by χ^2 test. All *P* are 2-sided: $P < 0.05$ is considered statistically significant.

Results

Demographic data relating to the 350 patients initially enrolled in this study are listed in Table 1. Man-woman ratios in the GU and DU groups were higher than that of the gastritis-only group. Mean age of patients with gastritis only was the highest of the 3 groups; that of patients with GU was next, and that of patients with DU was lowest. Mean body weight of patients with gastritis only was less than those of patients with GU and DU, perhaps because of the greater percentage of women in the gastritis-only group.

H. pylori Antibiotic Sensitivity

Culture tests showed no amoxicillin-resistant strains of *H. pylori* were present before treatment or after failure of eradication therapy. Based on culture tests and PCR-RFLP analysis for the 23S-rRNA mutation associated with clarithromycin resistance, 48 of 336 patients (14.3%) were found to be infected with clarithromycin-resistant *H. pylori* strains, all of which had the A2144G mutation. The distribution of these resistant strains was equal among the 3 endoscopic groups (gastritis only, 13%; GU, 14%; and DU, 18%; $P > 0.2$; Table 1).

IL-1β-511 and *CYP*2C19 Genotype Frequency

Distribution of the 3 *IL-1β*-511 genotypes in the 3 different endoscopic groups is listed in Table 1. The alleles at this locus were in Hardy-Weinberg equilibrium, with nonsignificant χ^2 values. There were no statistically significant differences between the gastritis-only, GU, or DU groups with regard to the prevalence of any of the *IL-1β*-511 genotypes ($P > 0.2$; Table 1). Equally, distribution of the *IL-1β*-511 genotypes was similar in men vs. women, patients with the 3 different *CYP*2C19 genotypes, and patients with clarithromycin-

Table 1. Distribution of Demographic, Bacterial, and Host Genetic Characteristics in the 350 Patients Comprising the Gastritis-Only, GU, and DU Groups

	Gastritis-only (n = 153)	GU (n = 110)	DU (n = 87)	*P*
Mean age (*yr*)	51.4 ± 8.8	48.7 ± 10.2	45.0 ± 10.2	<0.001
Mean body weight (*kg*)	60.7 ± 9.5	63.0 ± 8.8	64.0 ± 8.4	0.015
Sex (men/women)	113/40	105/5	81/6	<0.001
Bacterial clarithromycin sensitivity				
CAM-S (n = 299)	133 (87)	95 (86)	71 (82)	0.50
CAM-R (n = 51)	20 (13)	15 (14)	16 (18)	
Host *IL-1β*-511 genotypes				
C/C	43 (28)	28 (25)	30 (34)	0.60
C/T	72 (47)	58 (53)	40 (46)	
T/T	38 (25)	24 (22)	17 (20)	
Host *CYP2*C19 genotype				
homEM	53 (35)	39 (36)	27 (31)	0.97
hetEM	78 (51)	56 (51)	46 (53)	
PM	22 (14)	15 (14)	14 (16)	

NOTE. Values expressed as mean ± SD, number of patients/total number, or number (percent).
GU, gastric ulcer; DU, duodenal ulcer; homEM, homozygous extensive metabolizer; hetEM, heterozygous extensive metabolizer; PM, poor metabolizer; CAM-S, clarithromycin-sensitive strain of *H. pylori;* CAM-R, clarithromycin-resistant strain of *H. pylori.*

resistant or clarithromycin-sensitive *H. pylori* strains (Table 2).

Six different genotypic patterns for the *CYP2*C19 polymorphisms were observed. One hundred nineteen of 350 patients were homozygous for wt alleles in both exon 5 and exon 4 (wt/wt), 127 patients were heterozygous for the $CYP2C19_{m1}$ mutation without the $CYP2C19_{m2}$ mutation (wt/m1), 53 patients were heterozygous for the $CYP2C19_{m2}$ mutation without $CYP2C19_{m1}$ mutation (wt/m2), 16 patients were heterozygous for both the $CYP2C19_{m1}$ and $CYP2C19_{m2}$ mutations (m1/m2), 29 patients were homozygous for the $CYP2C19_{m1}$ mutation without the $CYP2C19_{m2}$ mutation (m1/m1), and 6 patients were homozygous for the $CYP2C19_{m2}$ mutation without the $CYP2C19_{m1}$ mutation (m2/m2). Based on these genotypes, patients were classified into the following 3 genotypic groups: the homEM group (wt/wt; n = 119), hetEM group (wt/m1 or wt/m2; n = 180), and PM group (m1/m1, m1/m2, or m2/m2; n = 51). There was no significant degree of linkage disequilibrium between the *CYP2*C19 and *IL-1β*-511 loci (data not shown).

Table 2. Distribution of *IL-1β*-511 Genotypes in 350 Patients Stratified on the Basis of Demographic, Bacterial, and Host Genetic Characteristics

	IL-1β-511 C/C (n = 101)	*IL-1β*-511 C/T (n = 170)	*IL-1β*-511 T/T (n = 79)	*P*
Mean age (*yr*)	48.9 ± 7.9	48.6 ± 11.1	49.9 ± 9.8	0.53
Mean body weight (*kg*)	62.9 ± 10.3	62.1 ± 8.5	61.7 ± 8.8	0.31
Sex				
Men	83 (82)	151 (89)	65 (82)	
Women	18 (18)	19 (11)	14 (18)	0.22
Endoscopic diagnosis				
Gastritis only (n = 153)	43 (43)	72 (42)	38 (48)	
GU (n = 110)	28 (28)	58 (34)	24 (30)	0.88
DU (n = 87)	30 (30)	40 (24)	17 (22)	
PPI used				
Omeprazole (n = 175)	47 (47)	80 (47)	48 (61)	
Lansoprazole (n = 175)	54 (53)	90 (53)	31 (39)	0.09
Host *CYP2*C19 genotype				
homEM (n = 119)	38 (38)	58 (34)	23 (29)	
hetEM (n = 180)	54 (53)	86 (51)	40 (51)	
PM (n = 51)	9 (9)	26 (15)	16 (20)	0.28
Bacterial clarithromycin sensitivity				
CAM-S (n = 299)	84 (83)	146 (86)	69 (87)	
CAM-R (n = 51)	17 (17)	24 (14)	10 (13)	0.71

NOTE. Values expressed as mean ± SD or number (percent).
GU, gastric ulcer; DU, duodenal ulcer; homEM, homozygous extensive metabolizer; hetEM, heterozygous extensive metabolizer; PM, poor metabolizer; CAM-S, clarithromycin-sensitive strain of *H. pylori;* CAM-R, clarithromycin-resistant strain of *H. pylori.*

Table 3. Univariate Analysis of Parameters Associated With Success or Failure of *H. pylori* Eradication in 336 Patients Who Completed the Study According to the Protocol

	Success of eradication	Failure of eradication	*P*
Mean age (*yr*)	49.3 ± 9.6	48.2 ± 12.3	0.50
Mean body weight (*kg*)	62.1 ± 8.8	63.0 ± 9.1	0.52
Sex			
Men	251 (87)	38 (13)	
Women	41 (89)	5 (11)	0.67
Endoscopic diagnosis			
Gastritis (n = 149)	133 (89)	16 (11)	
GU (n = 105)	91 (87)	14 (13)	
DU (n = 82)	69 (84)	13 (16)	0.53
PPI used			
Omeprazole (n = 169)	149 (88)	20 (12)	
Lansoprazole (n = 167)	144 (86)	23 (14)	0.59
IL-1β-511 genotype			
C/C (n = 97)	75 (77)	22 (23)	
C/T (n = 164)	147 (90)	17 (10)	
T/T (n = 75)	71 (95)	4 (5)	0.001
*CYP*2C19 genotype			
homEM (n = 113)	81 (72)	32 (28)	
hetEM (n = 172)	162 (94)	10 (6)	
PM (n = 51)	50 (98)	1 (2)	<0.001
Clarithromycin sensitivity			
CAM-S (n = 288)	269 (93)	19 (7)	
CAM-R (n = 48)	24 (50)	24 (50)	<0.001

NOTE. Values expressed as mean ± SD or number (percent).
GU, gastric ulcer; DU, duodenal ulcer; homEM, homozygous extensive metabolizer; hetEM, heterozygous extensive metabolizer; PM, poor metabolizer; CAM-S, clarithromycin-sensitive strain of *H. pylori;* CAM-R, clarithromycin-resistant strain of *H. pylori*.

*CYP*2C19 genotypes were distributed equally among the 3 endoscopic groups ($P > 0.2$; Table 1).

Eradication Rates

No clinically undesirable side effects of triple therapy were reported in this study. Of 350 patients enrolled initially, 336 patients completed the study according to the protocol. Fourteen patients were excluded from analysis because of poor compliance (n = 6) or refusal to undergo a second endoscopy (n = 8). The analyses presented next pertain to the 336 patients who completed the study successfully. Of these 336 patients, 293 patients (87.2%) were successfully cured of the infection, judged by negative ^{13}C-UBT, RUT, bacterial culture, and histological examination results, all performed at least 1 month after eradication therapy. In 43 patients (12.8%), eradication therapy was judged to have failed. Failure of eradication was distributed equally among the 3 endoscopic groups (gastritis-only, 11%; GU, 13%; and DU, 16%; $P > 0.2$; Table 3).

Factors Influencing Eradication Rates

Because all 3 endoscopic groups were similar in terms of eradication rates, *H. pylori* sensitivity to antibiotics, and distribution of *IL-1β*-511 and *CYP*2C19 genotypes, we combined the 3 groups (total, 336 patients) for the purpose of analyzing factors that influence eradication rates. Univariate analysis showed that 3 factors significantly influenced success of eradication therapy: *IL-1β*-511 genotype, *CYP*2C19 genotype, and *H. pylori* clarithromycin resistance (Table 3). Thus, 95% of patients with the *IL-1β*-511 T/T genotype and 90% of patients with the C/T genotype had *H. pylori* successfully eradicated compared with 77% of patients with the C/C genotype ($P = 0.002$ and $P = 0.011$, respectively; Figure 1). Of 75 subjects with the T/T genotype, eradication therapy failed in only 4 subjects compared with 22 of 97 subjects with the C/C genotype. In a logistic regression model including all parameters, odds ratios for successful eradication were 3.18 (95% confidence interval, 1.24–8.11; $P = 0.02$) and 4.24 (95% confidence interval, 1.14–15.76; $P = 0.03$) for the *IL-1β*-511 C/T and T/T genotypes, respectively, compared with the C/C genotype (Table 4).

Similarly, 98% of patients with the *CYP*2C19 PM genotype and 94% of those with the hetEM genotype

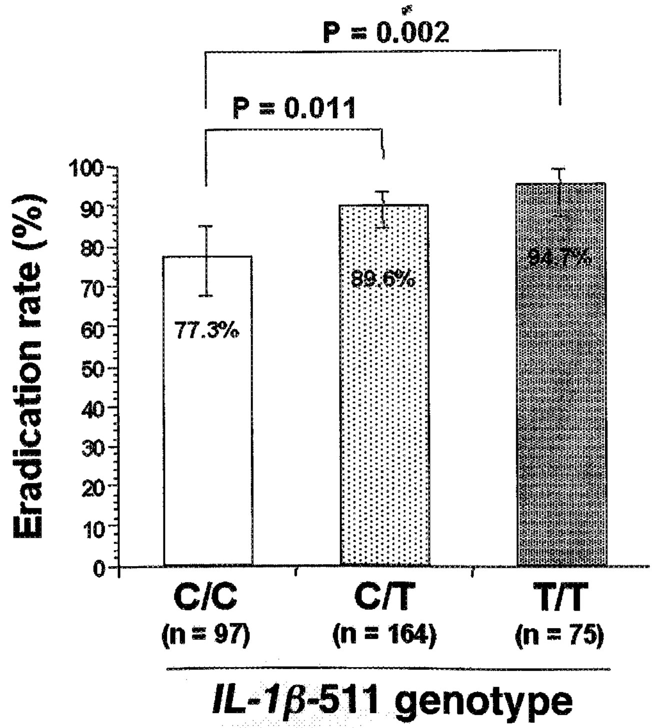

Figure 1. Eradication rates of *H. pylori* in the groups with the *IL-1β*-511 C/C, C/T, and T/T genotypes. *Bars* indicate 95% confidence intervals. The eradication rate in the group with the *IL-1β*-511 T/T genotype was highest, that in the *IL-1β*-511 C/T genotype group came next, and that in the *IL-1β*-511 C/C genotype group was the lowest.

Table 4. Logistic Regression Analysis of Parameters Associated With Success or Failure of *H. pylori* Eradication in 336 Patients Who Completed the Study According to the Protocol

Parameter	Odds ratio	95% CI	P
Age	1.03	0.99–1.1	0.19
Body weight	1.01	0.96–1.1	0.73
Sex			
Men (reference)	1.00		
Women	2.12	0.46–9.8	0.33
Endoscopic diagnosis			
Gastritis (reference)	1.00		
GU	0.60	0.22–1.7	0.34
DU	0.92	0.29–2.9	0.88
PPI			
Omeprazole (reference)	1.00		
Lansoprazole	0.88	0.36–2.2	0.78
*CYP*2C19 genotype			
homEM (reference)	1.00		
hetEM	9.10	3.3–24.9	<0.001
PM	97.76	8.8–1083.0	<0.001
Clarithromycin sensitivity			
CAM-R (reference)	1.00		
CAM-S	42.03	13.1–134.4	<0.001
IL-1β-511 genotype			
C/C (reference)	1.00		
C/T	3.18	1.2–8.1	0.02
T/T	4.24	1.1–15.8	0.03

CI, confidence interval; GU, gastric ulcer; DU, duodenal ulcer; homEM, homozygous extensive metabolizer; hetEM, heterozygous extensive metabolizer; PM, poor metabolizer; CAM-S, clarithromycin-sensitive strain of *H. pylori;* CAM-R, clarithromycin-resistant strain of *H. pylori.*

underwent successful eradication compared with 72% of patients with the homEM genotype ($P < 0.0001$ for both; Table 3). Of 51 subjects with the PM genotype, eradication failed in only 1 subject compared with 32 of 113 subjects with the homEM genotype. In a logistic regression model including all parameters, odds ratios for successful eradication were 9.01 (95% confidence interval, 3.32–24.94; $P < 0.0001$) and 97.76 (95% confidence interval, 8.82–1083.04; $P = 0.0002$) for the *CYP*2C19 hetEM and PM genotypes, respectively, compared with the homEM genotype (Table 4).

Finally, 93% of patients who harbored clarithromycin-sensitive *H. pylori* strains underwent successful eradication compared with only 50% of those who had clarithromycin-resistant strains. In a logistic regression model including all parameters, the odds ratio for successful eradication was 42.0 (95% confidence interval, 13.1–134.4; $P < 0.02$) for clarithromycin-sensitive compared with clarithromycin-resistant strains.

Effect of *IL-1β*-511 Genotype on Eradication Rate as a Function of *CYP2C19* Genotype Status and Clarithromycin Sensitivity

Table 5 lists eradication rates for 3 *IL-1β*-511 genotype groups as a function of *CYP*2C19 genotype status and clarithromycin sensitivity. In patients infected with clarithromycin-resistant strains, the *IL-1β*-511 T/T genotype significantly increased the eradication rate to 78%, which appeared greater than those for the *IL-1β*-511 C/C and C/T genotypes (35% and 50%, respectively; $P = 0.1195$). Similarly, the *CYP*2C19 PM genotype significantly increased the eradication rate to 89%, which was significantly greater than those for the homEM and hetEM genotypes (11% and 65%, respectively; $P < 0.0001$). In patients iffected with clarithromycin-sensitive strains, the *IL-1β*-511 T/T and C/T genotypes significantly increased eradication rates to 97% and 96%, respectively, compared with an eradication rate of 86% in patients with the C/C genotype ($P = 0.0096$). Similarly, the *CYP*2C19 PM and hetEM genotypes significantly increased eradication rates to 100% and 97% compared with 84% in patients with the homEM genotype ($P < 0.0001$). Thus, in both clarithromycin-sensitive and clarithromycin-resistant strains of *H. pylori*, having a *CYP*2C19 PM genotype and *IL-1β*-

Table 5. Summary of Eradication Rates for 3 *IL-1β*-511 Genotype Groups as Functions of *CYP*2C19 Genotype and Sensitivity of *H. pylori* to Clarithromycin

		IL-1β-511			
Sensitivity to clarithromycin	*CYP*2C19	C/C	C/T	T/T	P^a
Resistant (n = 48)	homEM	10.0% (1/10)	12.5% (1/8)	0.0% (0/1)	0.93
	hetEM	60.0% (3/5)	55.6% (5/9)	100% (3/3)	0.37
	PM	100% (2/2)	100% (5/5)	80% (4/5)	0.47
Sensitive (n = 288)	homEM	64.0% (16/25)[b]	89.6% (43/48)	95.4% (20/21)	0.005
	hetEM	95.8% (46/48)	98.6% (72/73)	97.1% (33/34)	0.63
	PM	100.0% (7/7)	100.0% (21/21)	100.0% (11/11)	

homEM, homozygous extensive metabolizer; hetEM, heterozygous extensive metabolizer; PM, poor metabolizer.
[a]χ^2 test.
[b]Significantly lower than C/T ($P = 0.013$) and T/T ($P = 0.013$, Fisher exact test).

511 proinflammatory genotype (T/T or C/T) significantly increases the chances of successful eradication.

Furthermore, each of these genotypes could enhance the chances of eradication in the absence of the other (Table 5). Finally, the effect of these 2 genotypes is most dramatic when comparing subjects with both *IL-1β*-511 T/T and *CYP*2C9 PM genotypes compared with subjects with both *IL-1β*-511 C/C and homEM genotypes. In this case, eradication rates increased from 10% to 80% in those with clarithromycin-resistant strains and 64% to 100% in those with clarithromycin-sensitive strains (Table 5).

Discussion

The present study shows that 3 important factors determine the success of eradication therapy based on a 1-week course including a PPI, clarithromycin, and amoxicillin. Two of these factors, namely, clarithromycin sensitivity and *CYP*2C19 genotype, have been described before,[18] and the present study confirms their significance. Our study reports for the first time that another host genetic factor, namely, *IL-1β* genotype, also has an important role in determining success of therapy. Thus, subjects with the most proinflammatory *IL-1β* genotype (−511 T/T) have a very high chance of successful eradication, even in the presence of clarithromycin-resistant strains. In subjects with an *IL-1β*-511 T/T genotype and CYP2C19 PM genotype, the risk for failure of eradication therapy is negligible.

Subjects with the *IL-1β*-511 T/T and C/T genotypes are at greater risk for developing achlorhydria in response to *H. pylori* infection.[40,42,46] We found that the median fasting intragastric pH was 6.5 in those with the T/T genotype and 3.8 in those with the T/C genotype, which was significantly higher than that in subjects with the C/C genotype (median, pH 2.4).[42] It is reasonable to assume that such high pretreatment intragastric pH levels in subjects with the proinflammatory *IL-1β*-511 genotypes would require little PPI effect to drive the pH even higher and maintain neutrality, in contrast to subjects with the C/C genotype. The more rapid achievement of neutral intragastric pH in subjects with the proinflammatory *IL-1β*-511 genotypes would increase the bioavailability of the 2 antibiotics that form part of this eradication regimen. This clearly increases the therapeutic efficacy of these antibiotics and is translated into a greater success rate at eradication. In subjects with the C/C genotype, the PPI has to be administered for a longer time and, presumably, in a greater dose to achieve similar levels of acid suppression.

In the present study, we found that the effect of the *IL-1β*-511 genotype on eradication rates was most apparent in patients with the *CYP*2C19 homEM genotype. This probably reflects that these subjects have lower plasma PPI levels (by virtue of the rapid metabolism of the drug) and are slower at inhibiting intragastric acidity in response to PPI therapy.[13,19–23,53,54] This is particularly the case during the first 3 days of dosing, as shown in a recent study by Saitoh et al.[55] As such, a proinflammatory and acid-lowering *IL-1β*-511 genotype has a much more marked effect in such subjects compared with those with a *CYP*2C19 hetEM or PM genotype, in whom the greater plasma PPI levels have a much more marked and rapid inhibitory effect.

The corollary to these observations is that subjects with the homEM and *IL-1β*-511 C/C genotypes will require a longer duration of eradication therapy (or greater PPI dose) to maximize chances of successful treatment because a high dose of a PPI (i.e., lansoprazole, 30 mg 4 times daily) could attain complete acid inhibition in *H. pylori*–negative homEMs.[23] Optimal PPI dose and duration of treatment remain to be tested in a prospective manner, but results are likely to have a major impact on clinical practice in Asian populations, in whom the frequency of *CYP*2C19 mutations are high (13%–24%).[16,56–58]

In this study, we found no amoxicillin-resistant strains in any of our subjects. This is in keeping with epidemiological data available from many geographic areas.[8,51,59] Conversely, we found that nearly 15% of our *H. pylori* isolates are resistant to clarithromycin. Murakami et al.[59] also reported that 23.3% of *H. pylori* isolate was resistant to clarithromycin. The incidence of clarithromycin-resistant strains of *H. pylori* in Japan is unacceptably high, which causes understandable anxiety, particularly in view of the ever-expanding indications for use of this antibiotic. For this reason, it is essential to maximize our ability to successfully eradicate *H. pylori* with first-line therapy. If this entails giving eradication therapy for a longer period in some subjects who have certain *IL-1β* or *CYP*2C19 genotypes, that would be an acceptable price to pay to avoid the expansion of clarithromycin resistance in our populations.

In conclusion, our results indicate that genotyping of the *IL-1β* polymorphism could be a prognostic indicator of the success or failure of a PPI-based eradication therapy, especially in subjects with the *CYP*2C19 homEM genotype. Combination analysis of *IL-1β* polymorphism with *CYP*2C19 genotype and bacterial resistance to antibacterial agents could predict the therapeutic outcome to treatment with standard regimens and could be useful for optimal treatment for *H. pylori* infection. The clinical usefulness, as well as cost-effectiveness, of this genotyping test for *H. pylori* eradication therapy remains to be determined under an adequate study design in a prospective manner.

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Supported in part by grants-in-aid for Scientific Research from Yokoyama Rinshoyakuri Zaidan, and by a grant-in-aid for the Center of Excellence (COE) from the Ministry of Education, Culture, Sports, Science and Technology, Japan, and from the Ministry of Health, Labour, and Welfare, Japan.

The authors thank the endoscopy staff, including Satoko Takebayashi, Hiroko Murakami, Kyoko Nishitani, and Saori Itoh, for their assistance.